National Comprehensive Cancer Network®

Monthly Oncology Tumor Boards:
A Multidisciplinary Approach to Individualized Patient Care

Diffuse Large B-Cell Lymphoma in Young Adults

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Moderated by Rose K. Joyce
NCCN, Conferences and Meetings Department

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Case 1: Young woman with a mediastinal mass

- 23-year-old woman presents with dry non-productive cough with a recent history of 8 pounds of unexplained weight loss. She presents to the local UrgiCenter where a respiratory PCR was positive for metapneumovirus and she is managed conservatively. She has a worsening cough and 5 pounds of further weight loss. She returns and a CXR reveals a large mediastinal mass. She is referred to a pulmonologist and the mass is confirmed by CT of the chest with maximal diameter of 11 cm. Transbronchial FNA reveals large atypical cells with expression of CD30 "consistent with classical Hodgkin lymphoma".
- She is referred to you. You recommend:
  1. Completion of pretreatment evaluation and ABVD + ISRT
  2. Completion of pretreatment evaluation and ABVD
  3. Completion of pretreatment evaluation and escBEACOPP
  4. Completion of pretreatment evaluation with mediastinoscopy

Case 1: Continued

- She undergoes mediastinoscopy and there are large cells with areas of sclerosis. The neoplastic cells EXPRESS CD20, OCT-2, BOB.1, CD30 (weak), CD23, TRAF-1 and c-REL and DO NOT EXPRESS CD10, CD15, MUM1/IRF4.
- The diagnosis is most consistent with:
  1. Diffuse large B-cell lymphoma, NOS
  2. Primary mediastinal large B-cell lymphoma
  3. Classical Hodgkin lymphoma, nodular sclerosing type
  4. Mediastinal grey zone lymphoma

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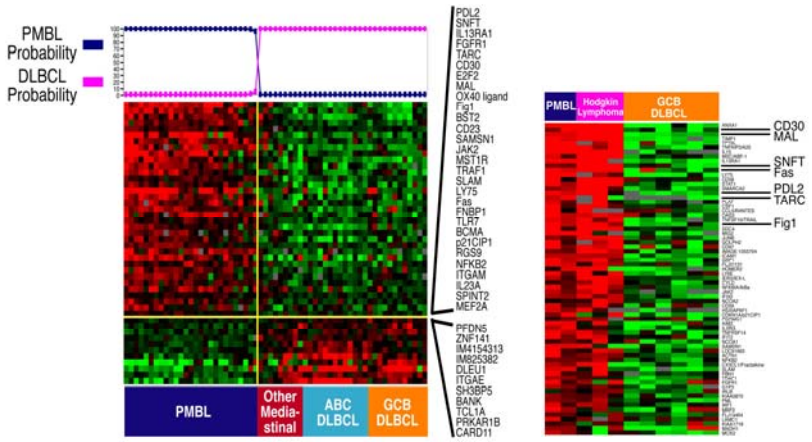
Pathology of Primary Mediastinal Diffuse Large B-Cell Lymphoma (PMBL)

PMBL: Gene Expression Profiling Identifies Relationship Between PMBL and cHL

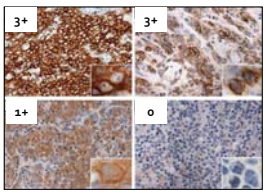


Lenz G, Staudt LM. N Engl J Med 2010;362:1417-1429

PMBL: Immunohistochemistry (IHC) Including Expression of PD-L2

- **Markers distinguishing DLBCL v PMBL:**
  - MAL; phosphorylated-STAT6; p63; TRAF1; activated (nuclear) cRel; TNFAIP2; CD23; CD200; PD-L2
- **Abnormalities involving chromosome 9p24.1:**
  - PMBL (70%); cHL (30%); DLBCL (rare)
- **Potential key genes at 9p24.1:**
  - *PDCD1LG2*, *CD274*, *JAK2*, and *JMJ2DC*
  - Amplification of 9p24.1 is often associated with increased transcription of all 4 genes
  - Gene expression profiling studies indicate relative overexpression of PD-L2 typically exceeds that of PD-L1 in PMBL

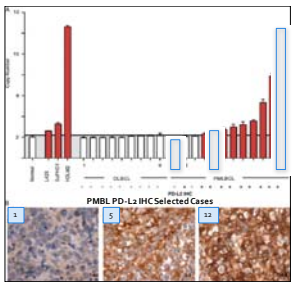
IHC Scoring



Diagnosis	N	Positive* n (%)	Negative n (%)
PMBL	32	23** (72)	9 (28)
DLBCL	37	1 (3)	36 (97)

*Membranous PD-L2 >20% 1-3+, **3+ 78%, >60% 83%

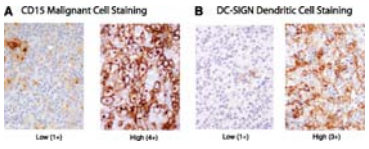
PD-L2 Copy Number and IHC Scoring

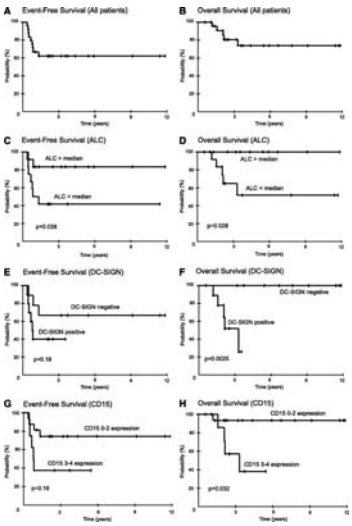


Min et al., Amer J Surg Path (2014), 38, 1715–1723;
Lenz et al., ASH annual meeting, 2007;
Lenz G, Staudt LM. N Engl J Med 2010;362:1417-1429

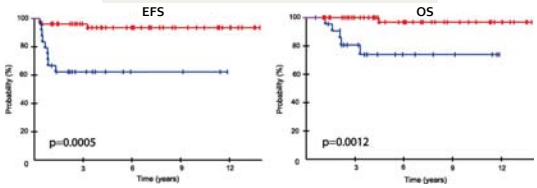
Mediastinal Grey Zone Lymphoma (MGZL): An entity between HL and PMBL with an inferior outcome

- **MGZL**
  - **Morphology**: May be more like cHL (~63%) or PMBL (~33%); some may appear composite (~4%)
  - **B-Cell:** CD20+ (strong ~70%); BCL6 (~85%)
  - **HL:** CD30 (100%); CD15 (~50%, variable)
  - **Infiltrating Dendritic Cells**: (measured by expression of dendritic cell–specific intercellular adhesion molecule-3-grabbing non-integrin [DC-SIGN]) ~50%, variable.





Outcome with DA-EPOCH R PMBL and MGZL



Wilson et al. Blood (2014);124:1563-1569

Case 1: Continued

- Your treatment recommendation for this patient is:
  1. R-CHOP
  2. R-CHOP + involved site radiation therapy
  3. DA-EPOCH-R
  4. Sequential R-CHOP/ICE

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PMBL: Therapy

Dose-adjusted (DA)-EPOCH-R

Drug	Dose
Rituximab	375 mg/m² day 1 IVPB
Doxorubicin	10 mg/m²/day x 4 by CI
Vincristine	0.4 mg/m²/day x 4 by CI
Etoposide	50 mg/m²/day x 4 by CI
Cyclophosphamide	750 mg/m² day 5 IVBP
Prednisone	60 mg/m² BID days 1-5 oral
Filgrastim*	Weight-adjusted dose starting day 5 until ANC > 5000/µL

*Recent data from MSKCC showed identical rate of dose-adjustment with filgrastim or pegfilgrastim

- Dosed every 21 days if ANC > 1/µL and PLTS > 100Kµl
- Dose-adjusted based on ANC nadir:
  - >500/µL, increase cytotoxic drugs by 20%
  - <500/µL for 1-3 days, no change
  - <500/µL for >3 days or FN, decrease cytotoxic drugs by 20%

Wilson, J Clin Oncol 2008 26: 2717-2724; Lunning et al. Clinical Lymphoma Myeloma and Leukemia 2014;14:S144.

PMBL: DA-EPOCH-R Patient Characteristics

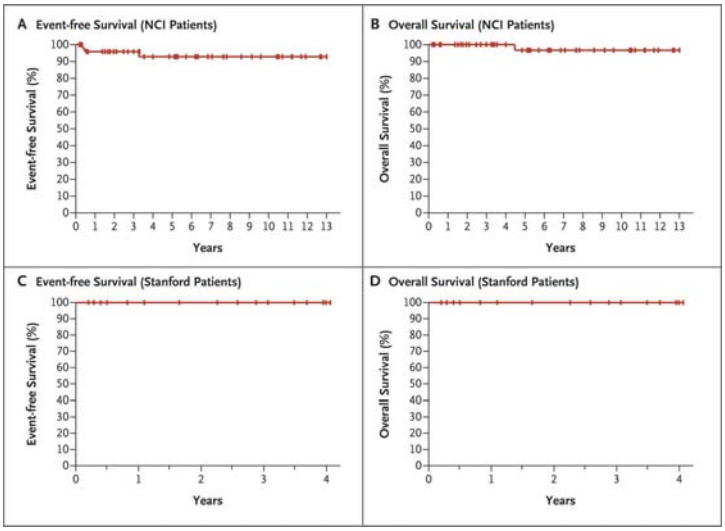
Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Prospective NCI Cohort (N=51)	Retrospective Stanford Cohort (N=16)	P Value between Study Cohorts
Female sex — no. (%)	30 (59)	9 (56)	1.00
Age — yr			0.04
Median	30	33	
Range	19–52	23–68	
Bulky tumor, ≥10 cm			0.57
Patients — no. (%)	33 (65)	9 (56)	
Maximal diameter range — cm	5–18	7–18	
Stage IV disease — no. (%)	15 (29)	7 (44)	0.36
Elevated lactate dehydrogenase level — no. (%)	40 (78)	11 (69)	0.51
Extranodal site — no. (%)	27 (53)	3 (19)	0.02
Pleural effusion — no. (%)	24 (47)	10 (62)	0.39
CD20+ malignant cells — no. (%)	51 (100)	16 (100)	1.00
BCL6+ malignant cells — no. (%)	33/37 (89)	ND	ND

* BCL6 denotes the B-cell lymphoma 6 protein, NCI National Cancer Institute, and ND not done.

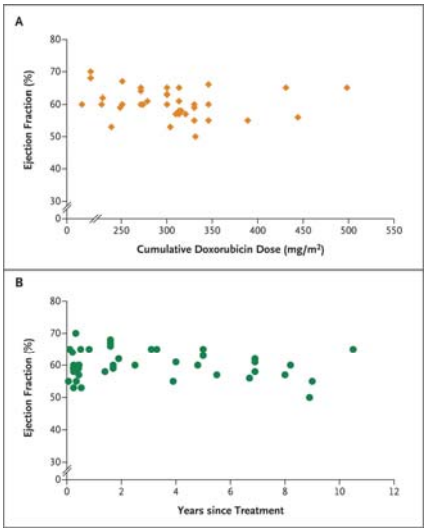
Dunleavy et al. N Engl J Med (2013) 368:1408-1416

PMBL: DA-EPOCH-R PFS and OS



Dunleavy et al. N Engl J Med (2013) 368:1408-1416

PMBL: DA-EPOCH-R impact on cardiac ejection fraction



Dunleavy et al. N Engl J Med (2013) 368:1408-1416

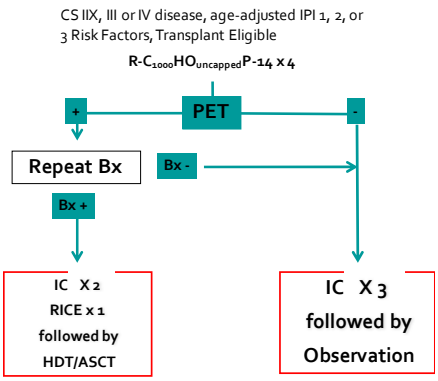
PMBL: FDG-PET-CT Findings after DA-EPOCH-R

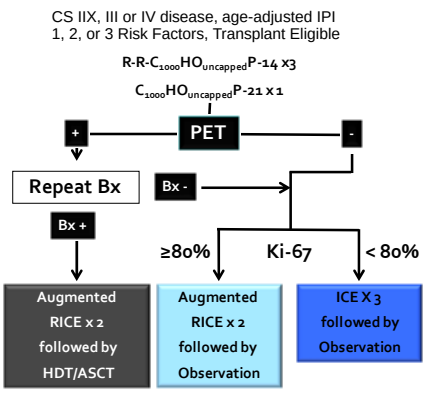
Table 2. FDG-PET-CT Findings after DA-EPOCH-R Therapy in the Prospective NCI Cohort.*

Lymphoma Status	Maximum Standardized Uptake Value				FDG-PET-CT Performance
	≤Value in Mediastinal Blood Pool (N=18)	>Value in Mediastinal Blood Pool (N=18)			
		total	value <5	value ≥5	
					percent
No disease (no. of patients)	18	15	12	3	
Disease recurrence (no. of patients)	0	3	0	3	
Sensitivity					100
Specificity					54
Positive predictive value					17
Negative predictive value					100

Dunleavy et al. N Engl J Med (2013) 368:1408-1416

MSKCC 01-142/08-146: DLBCL-Risk Adapted for Therapy

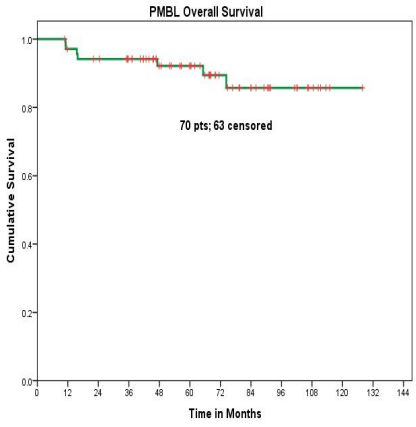


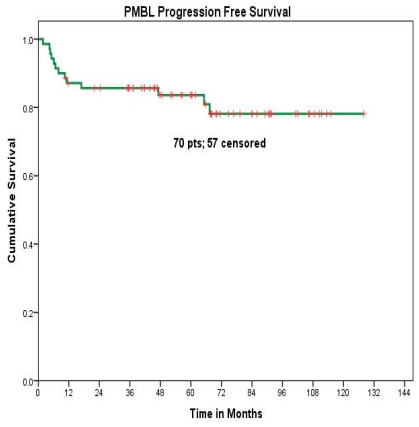


- Prospective, biopsy controlled determination of "positive PET"
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM
- Two studies with highly similar outcomes, combined analysis

Moskowitz C, et al. Blood 2010;116:Abstract 420

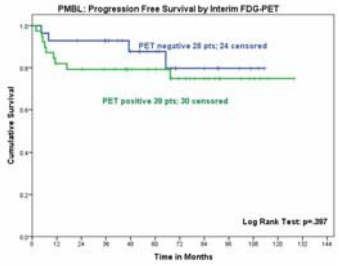
Sequential R-CHOP ➜ ICE (MSKCC 01-142 and 08-026) PMBL Patients: Outcomes

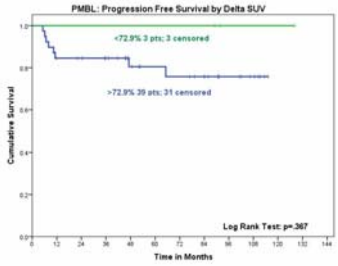


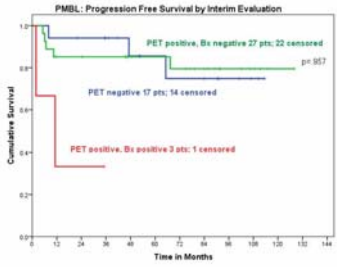


Moskowitz C, et al. Blood 2010;116:Abstract 420

Sequential R-CHOP ➜ ICE (MSKCC 01-142 and 08-026) PMBL Patients: Interim FDG-PET







Moskowitz C, et al. Blood 2010;116:Abstract 420

PMBL Principles

- More frequent in young women
- Important to avoid radiation therapy to minimize risk of breast cancer and late cardiovascular complications
- DA-EPOCH-R or sequential R-CHOP/ICE are reasonable options
  - No randomized trials are available
- Large scale trials have not been performed with either regimen
- Immune checkpoint inhibitors have a rationale in PMBL and need to be more fully evaluated

Case 2: Young man with a cervical mass

- 32-year-old man found a "lump in my neck when I was shaving a month ago". He presented to his PCP who identified a 2.5 x 2 cm firm, non-tender left cervical mass. The mass did not resolve after a course of amoxicillin-clavulanate. He is referred for biopsy demonstrating diffuse effacement of the nodal architecture by large cells that EXPRESS CD20, CD10, MUM1/IRF4 and DO NOT EXPRESS CD5, BCL6. Ki-67 stains 70% of the large cells. The diagnosis is:
  1. DLBCL, germinal center
  2. DLBCL, non-germinal center
  3. PMBL
  4. Follicular lymphoma, grade 3B

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Pathology of DLBCL

WHO Classification of Lymphoid Neoplasms (2008)

Precursor

- B lymphoblastic leukaemia/lymphoma
- B lymphoblastic leukaemia/lymphoma, NOS
- B lymphoblastic leukaemia/lymphoma
- with recurrent genetic abnormalities
- B lymphoblastic leukaemia/lymphoma
- with t(9;22)(q34;q11.2); *BCR-ABL1*
- B lymphoblastic leukaemia/lymphoma
- with t(v;11q23); *MLL* rearranged
- B lymphoblastic leukaemia/lymphoma
- with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)*
- B lymphoblastic leukaemia/lymphoma
- with hyperdiploidy
- B lymphoblastic leukaemia/lymphoma
- with hypodiploidy (hypodiploid ALL)
- B lymphoblastic leukaemia/lymphoma
- with t(5;14)(q31;q32); *IL3-IGH*
- B lymphoblastic leukaemia/lymphoma with
- t(1;19)(q23;p13.3); *E2A-PBX1; (TCF3-PBX1)*
- T lymphoblastic leukaemia/lymphoma

Indolent B

- Chronic lymphocytic leukaemia/ small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- *Splenic lymphoma/leukaemia, unclassifiable**
- *Splenic diffuse red pulp small B-cell lymphoma*
- *Hairy cell leukaemia-variant*
- Lymphoplasmacytic lymphoma
- Waldenström's macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- *Paediatric nodal marginal zone lymphoma*
- Follicular lymphoma
- *Paediatric follicular lymphoma*
- Primary cutaneous follicle centre lymphoma

Aggressive B

- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- *EBV positive DLBCL of the elderly*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- *B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma*
- *B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma*

Mature T/NK

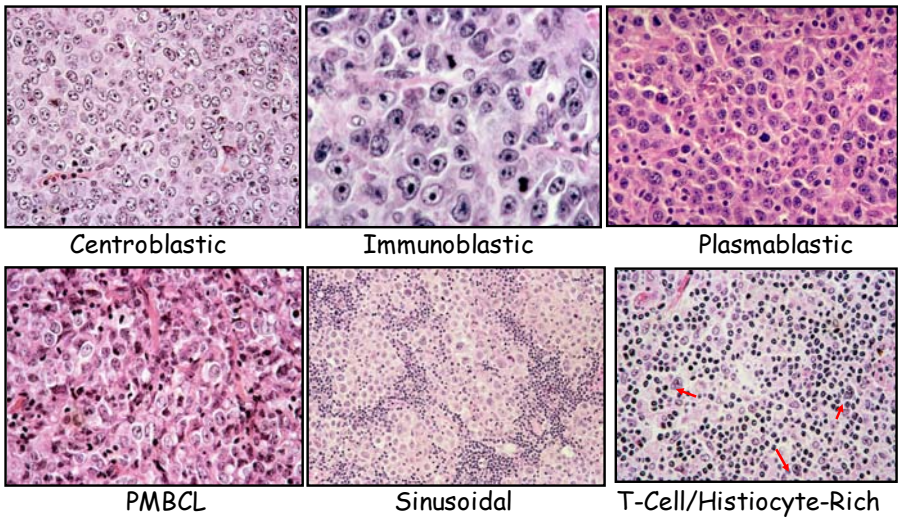
- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- *Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK cell leukaemia
- Systemic EBV positive T-cell lymphoproliferative
- disease of childhood
- Hydroa vaccineforme-like lymphoma
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, *ALK* positive
- *Anaplastic large cell lymphoma, ALK negative*

HL and PTLD

- HODGKIN LYMPHOMA
  - Nodular lymphocyte predominant Hodgkin lymphoma
  - Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte depleted classical Hodgkin lymphoma
- POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)
  - Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like PTLD
  - Polymorphic PTLD
  - Monomorphic PTLD (B- and T/NK-cell types) #
  - Classical Hodgkin lymphoma type PTLD #

To be updated in 2017

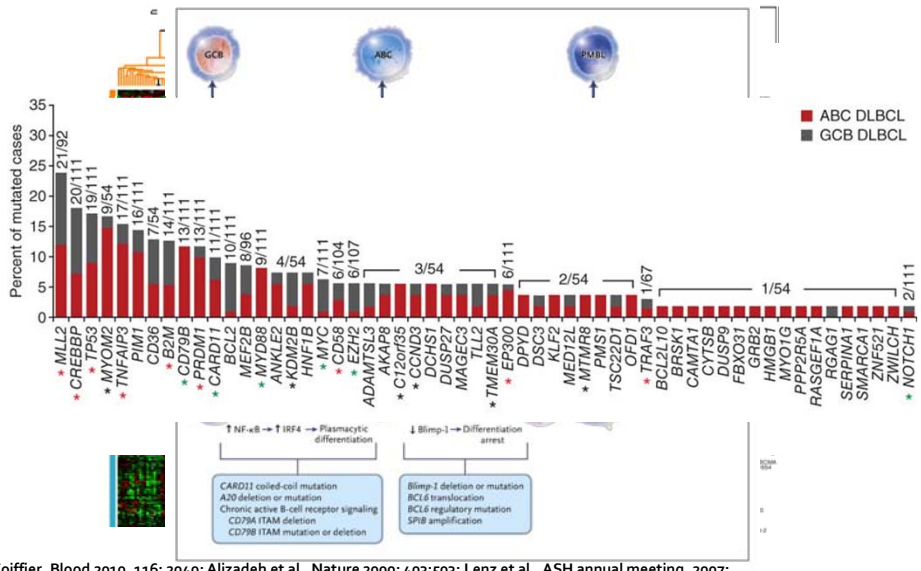
Morphologic Heterogeneity of DLBCL



DLBCL, NOS and other Large B-cell Disorders: WHO 2008

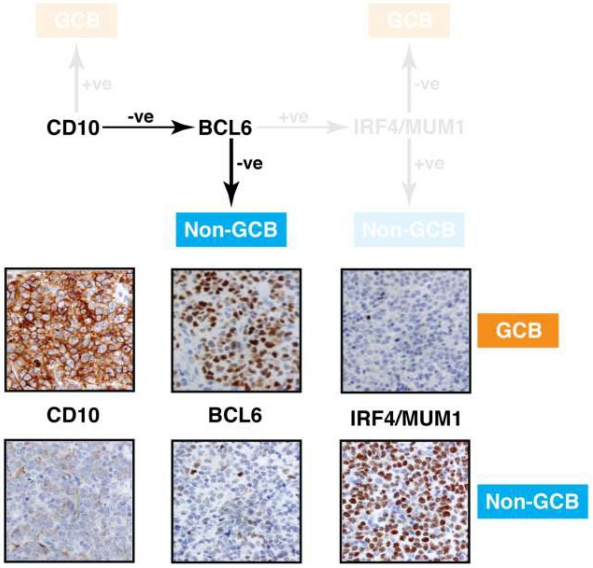
- Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group of disorders with varied natural history, genetic abnormalities, and response to therapy
- DLBCL, NOS: 31%
- Primary mediastinal (thymic) large B-cell lymphoma: 2%
- Variants: ~3%
  - T-cell/histiocyte rich large B-cell lymphoma
  - Primary cutaneous DLBCL, leg type
  - EBV positive DLBCL of the elderly
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis (EBV)
  - Intravascular large B-cell lymphoma
  - ALK positive large B-cell lymphoma
  - Primary CNS large B cell lymphoma

Tumor Heterogeneity in DLBCL



Coiffier, Blood 2010, 116: 2040; Alizadeh et al . Nature 2000; 403:503; Lenz et al., ASH annual meeting, 2007; Lenz G, Staudt LM. N Engl J Med 2010;362:1417-1429, Pasqualucci, Nat Gen 2011;43:830.

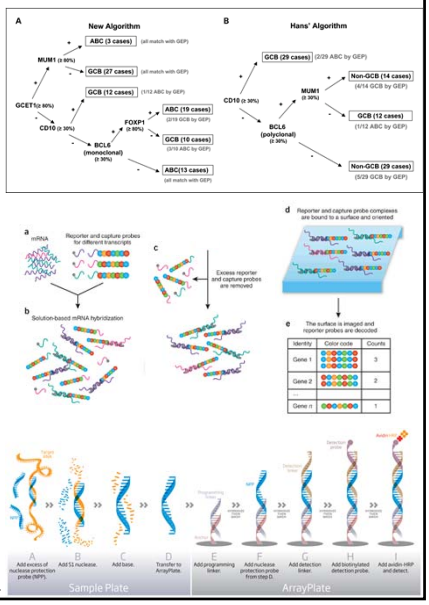
DLBCL: Cell of Origin (COO) by Hans Model



Hans et al. Blood 2004;103(1):275-82.

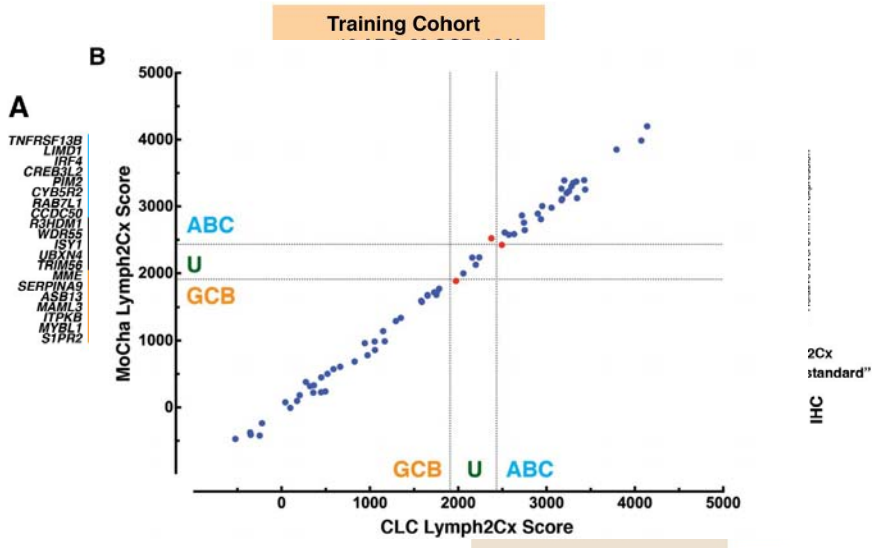
Cell of Origin: Immunohistochemistry v GEP

- There are several models for determination of cell of origin (COO)
  - They lack precision but can be used to enrich populations for GC or non-GC
- RNA-based gene expression profiling (GEP) is a research tool, not useful in clinical practice
- Robust platforms that use formalin-fixed, paraffin-embedded tissue are need for COO determination
  - Hybrid capture/fluorescent reporter
  - Hybrid capture/S1 nuclease
  - Microfluidic PCR arrays



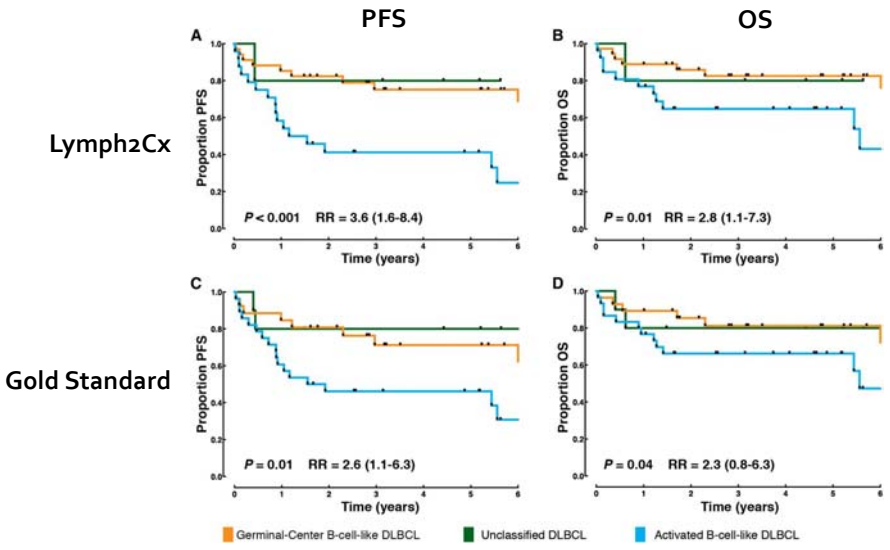
Choi et al, CCR 2009; 15:5494; Scott D W et al. Blood 2014;123:1214; Rimsza et al. CCR 2011;17:3727; Zelenetz et al. Blood 2013;122:Abstract 3017.

Performance of the Lymph2Cx assay in the independent validation cohort



Scott D W et al. Blood 2014;123:1214-1217

Patient outcomes according to COO in the independent validation cohort



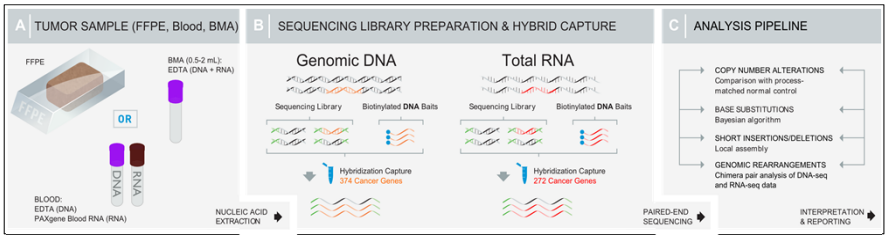
Scott D W et al. Blood 2014;123:1214-1217

Value of the Lymph2Cx assay

- It is a robust 20-gene predictor of GCB vs ABC built for FFPET samples
- Accurately assigns cell-of-origin categories
- Inexpensive (< $40) and can be done in less than 36 hours
- It is highly reproducible between laboratories
- It retains prognostic power compared to fresh tissue-based GEP

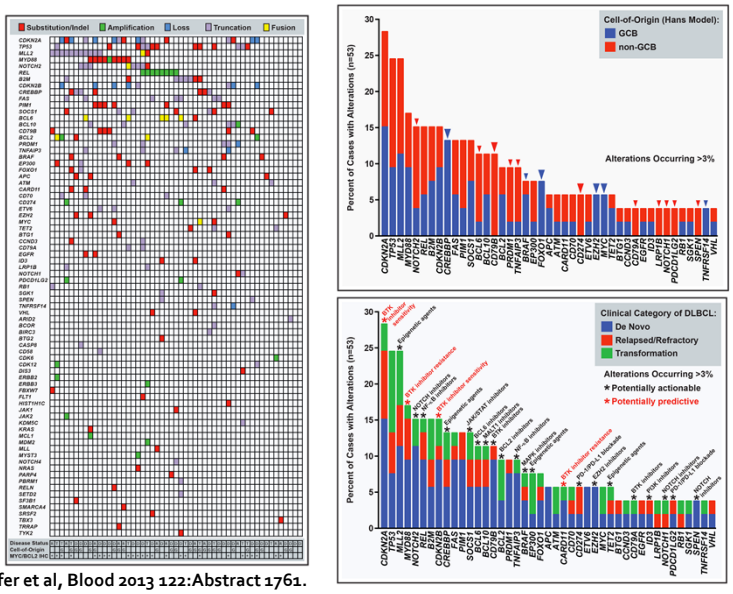
Scott D W et al. Blood 2014;123:1214-1217

Next Generation Sequencing of Commonly Mutated Genes: "FISH" for Genomics



- Sequencing a limited number of genes is to whole genome sequence as FISH is to cytogenetics
- Sequencing limited number of genes allows for greater "depth" of sequencing
  - Whole genome sequencing has coverage of 10-50x
  - Hybrid capture on limited genes (300-600) has coverage of 300-500x
  - Permits identification of small clones within a population of tumor cells

Targeted Sequencing in DLBCL: "FISH" for Genomics



Intlekofer et al, Blood 2013 122:Abstract 1761.

Case 2: Young man with a cervical mass

- Your treatment recommendation is:
  1. R-CHOP
  2. DA-EPOCH-R
  3. Sequential R-CHOP/ICE
  4. Clinical trial of lenalidomide and R-CHOP

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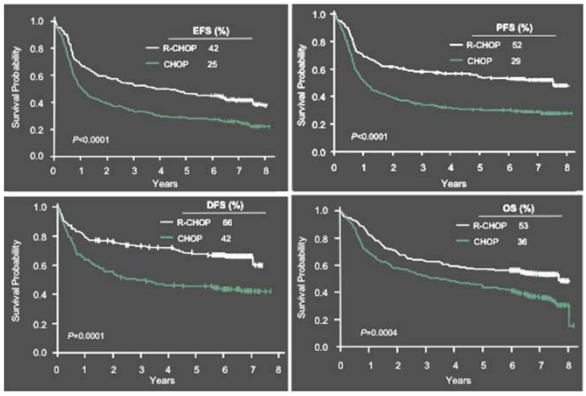
Clinical Management

International Standard of Care: R-CHOP

Rituximab 375 mg/m² day 1
Cyclophosphamide 750 mg/m² day 1
Doxorubicin 50 mg/m² day 1
Vincristine 1.4 mg/m² day 1 (2 mg max)
Prednisone 40 mg/m² (or 100 mg) daily x 5

Age > 60
Pegfilgrastim 6 mg subcut day 2

Original Gela LNH 98-5 confirmed in multiple studies



Coiffier et al. ASCO 2007;Abstract 8009.

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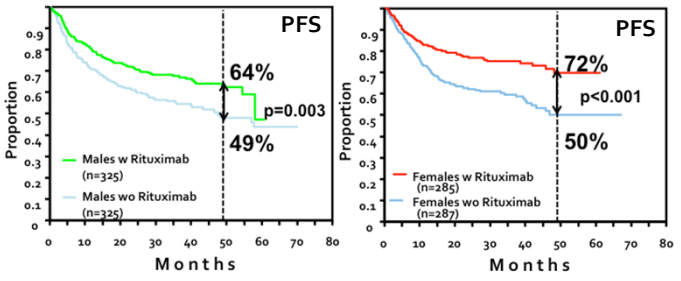
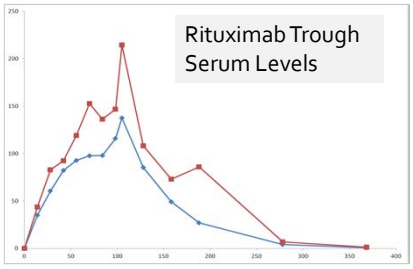
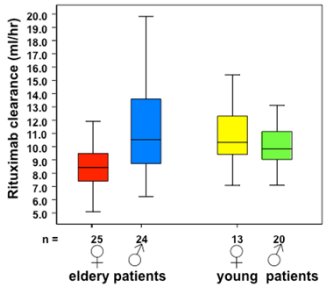
Is the dose of rituximab optimal? SEXIE-R-CHOP-14

RICOVER-60: Do difference in rituximab PK account for Male v Female outcome differences



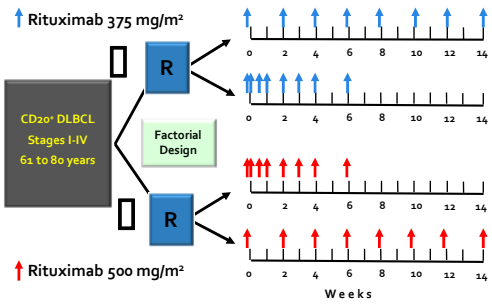


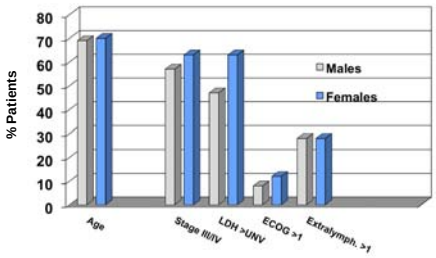


Older woman are the outliers

Pfreunschuh et al. ASCO 2014; Müller et al., Blood 2012, Pfreundschuh et al., Blood 2014

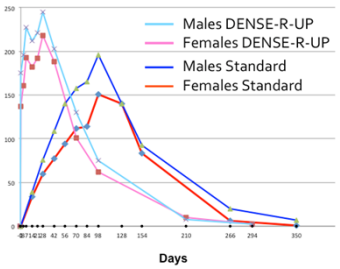
SEXIE-R-CHOP-14: Study Design and demographics

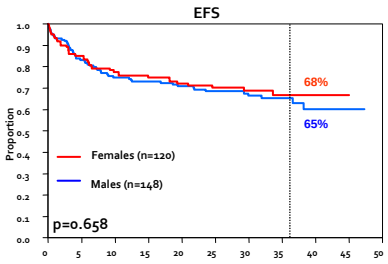


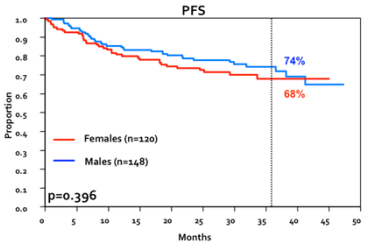


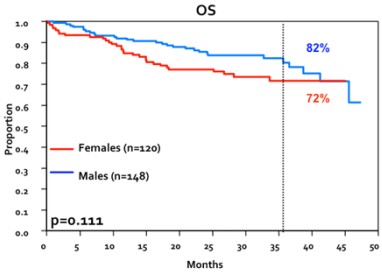
Pfreundschuh et al., Blood 2014

Equalizing rituximab exposure improves outcomes in men versus women >65









Pfreundschuh et al., J Clin Oncol 2014;32 (15_suppl):Abstract 8501.

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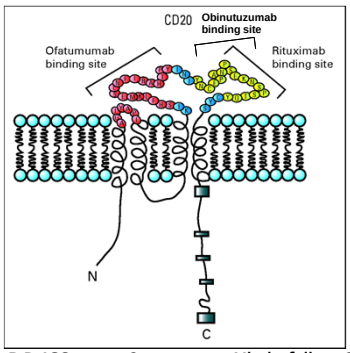
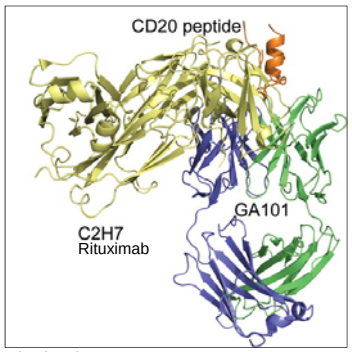
Alternative anti-CD20 antibody: Obinutuzumab

Comparison of FDA-approved anti-CD20 antibodies

	Rituximab	Ofatumumab	Obinutuzumab
Type	I	I	II
Apoptosis	+	-/+	++
ADCC	++	+/-	+++
Complement fixation	++	+++	+/-





Cheson B D JCO 2010;28:3525-3530; Niederfellner G et al. Blood 2011;118:358-367

GATHER (GAO4915g): Study design

Previously untreated DLBCL (n = 100) → **Obinutuzumab (GA101) x 8 cycles + CHOP x 6 cycles**

Obinutuzumab: 1,000 mg d1, d8, d15, cycle 1; d1, cycles 2–8, every 21 days
CHOP: cyclophosphamide 750 mg/m^2 d1, doxorubicin 50 mg/m^2 d1, vincristine 1.4 mg/m^2 d1, prednisone 100 mg/day d1–5; cycles 1–6, every 21 days

Primary endpoint	Secondary endpoints	Exploratory analyses
• ORR (CR + PR)	• PFS • Response duration • PK • Pharmacodynamics • Safety • Biomarkers	• Overall survival • Prognostic value of FDG-PET • FcγR polymorphism status

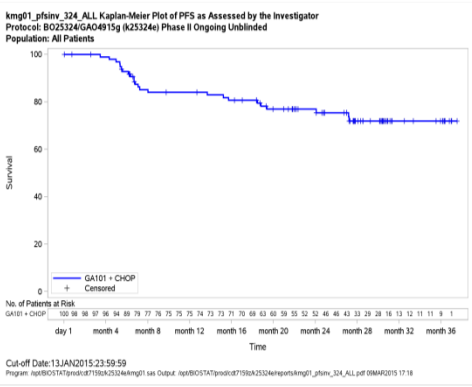
Evaluation

- Baseline and end of treatment FDG-PET scans, as well as CT scans after cycles 4 and 8 during study treatment
- FDG-PET scan will be performed after cycle 1 in the first 40 patients and after cycle 2 in the second 40 patients to explore its value in predicting patient outcomes
- Clinical tumour assessments will be performed every 3 months for 24 months, and then every 6 months for a further 12 months

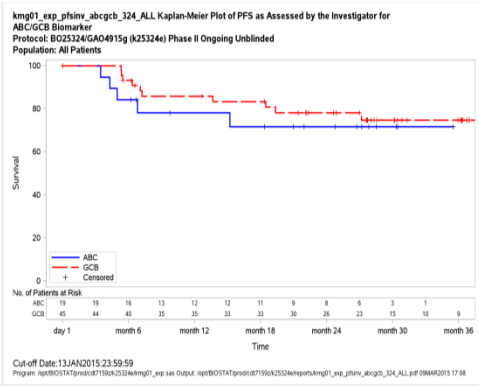
Zelenetz et al, ASH 2013: Abstract 1820; manuscript in preparation

Obinutuzumab-CHOP (G-CHOP) for DLBCL, median follow up 28 months

All Patients



By Cell of Origin*



*Cell of origin determined by microfluidic PCR (microfluidic dynamic arrays) using a modified Wright classifier

Zelenetz et al, ASH 2013; Abstract 1820; manuscript in preparation

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Alternatives to CHOP + anti-CD20 antibody

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Infusional Therapy: DA-EPOCH-R

Dose-Adjusted (DA)-EPOCH-R

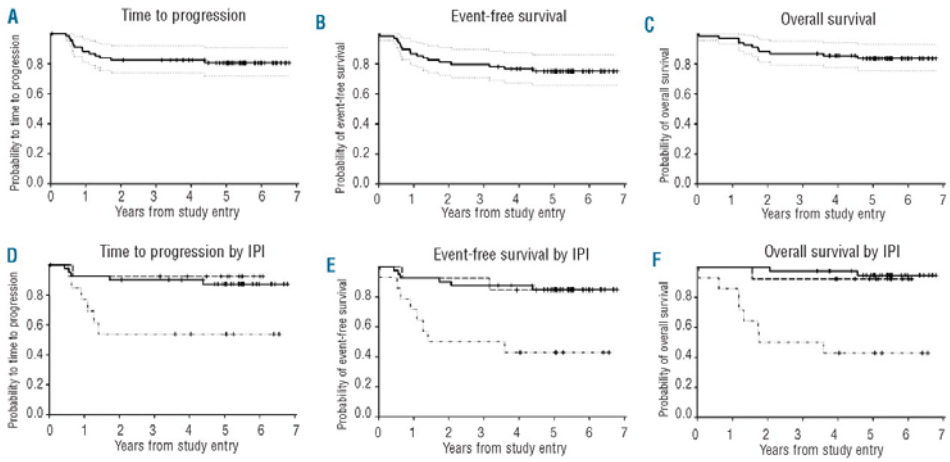
Drug	Dose
Rituximab	375 mg/m² day 1 IVPB
Doxorubicin	10 mg/m²/day x 4 by CI
Vincristine	0.4 mg/m²/day x 4 by CI
Etoposide	50 mg/m²/day x 4 by CI
Cyclophosphamide	750 mg/m² day 5 IVBP
Prednisone	60 mg/m² BID days 1-5 oral
Filgrastim*	Weight-adjusted dose starting day 5 until ANC > 5000/μL

*Recent data from MSKCC showed identical rate of dose-adjustment with filgrastim or pegfilgrastim

- Dosed every 21 days if ANC > 1/μL and PLTS > 100KμL
- Dose-adjusted based on ANC nadir:
  - >500/μL, increase cytotoxic drugs by 20%
  - <500/μL for 1-3 days, no change
  - <500/μL for >3 days or FN, decrease cytotoxic drugs by 20%

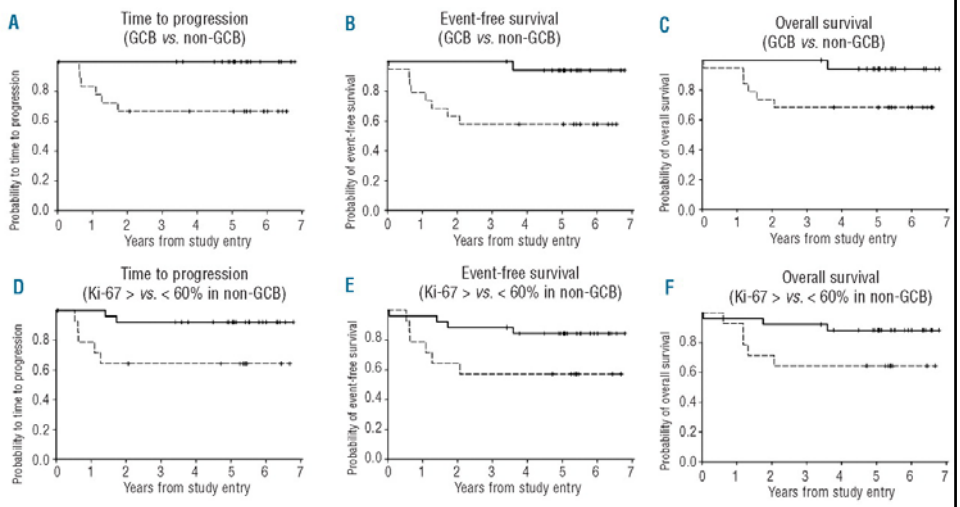
Wilson, J Clin Oncol 2008 26: 2717-2724; Lunning et al. Clinical Lymphoma Myeloma and Leukemia 2014;14:S144.

CALGB 59910: Multi-center DA-EPOCH-R, Outcomes



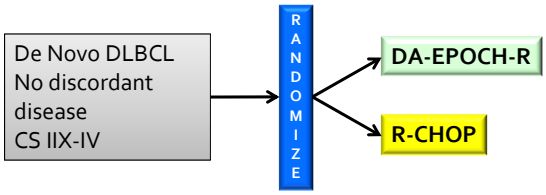
Wilson W H et al. Haematologica 2012;97:758-765

CALGB 59910: Multi-center DA-EPOCH-R, Outcomes by biomarkers



Wilson W H et al. Haematologica 2012;97:758-765

CALGB 50303: DA-EPOCH-R vs RCHOP21



n= 478 patients (239 per treatment arm)

- OBJECTIVES:
  - Primary
    - EFS untreated de novo DLBCL treated with RCHOP vs DA-R-EPOCH
    - Determine molecular predictors of outcome (using molecular profiling) in patients treated with these regimens.
  - Secondary
    - Compare ORR and OS
    - Compare the toxicity of these regimens in these patients.
    - Correlate the clinical parameters (i.e., toxicity, response, survival outcomes, and laboratory results) with molecular profiling in patients treated with these regimens.
    - Determine the use of molecular profiling for pathological diagnosis

FULLY ACCRUED, AWAITING EVENTS

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DLBCL: R-CHOP-21 or R-CHOP-14?

R-CHOP-14 v R-CHOP-21

- Three trials
  - GELA
    - Growth factor left to the discretion of the investigation
    - Dose intensity was poor on the R-CHOP-14 arm
    - No difference in PFS/OS
    - Toxicity favors R-CHOP-21
  - UK NCRI Lymphoma Clinical Study Group (CRUKE/03/019)
    - Growth factor as per the described regimens (R-CHOP-14 mandatory, R-CHOP-21 as clinically indicated
    - No difference in PFS/OS
    - Toxicity favors R-CHOP-14
  - DHLSG
    - Results not yet reported

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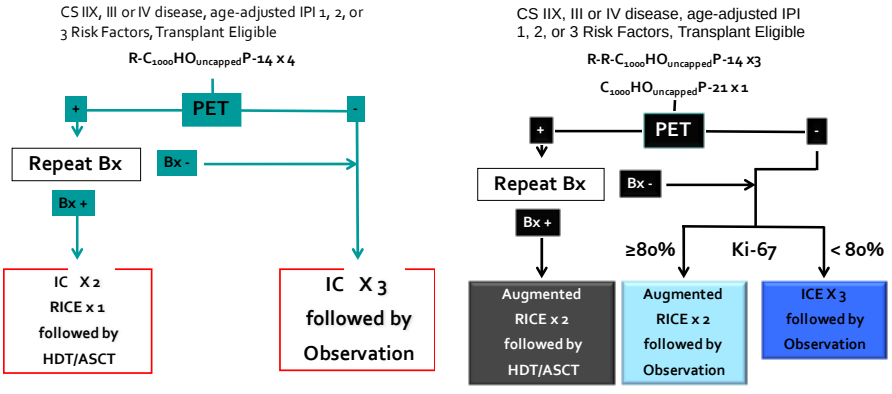
Sequential Non-cross resistant chemotherapy

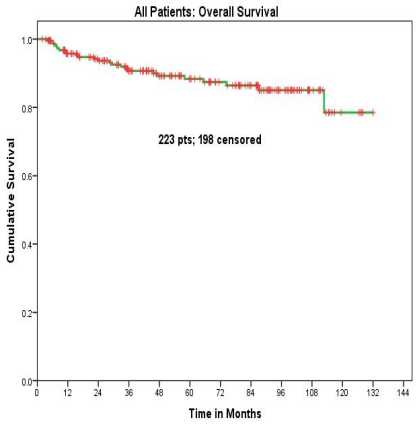
MSKCC 01-142/08-146: DLBCL-Risk Adapted for Therapy

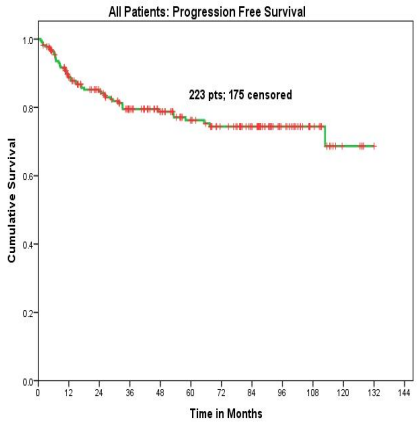


- Prospective, biopsy controlled determination of "positive PET"
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM
- Two studies with highly similar outcomes, combined analysis

Moskowitz C, et al. Blood 2010;116:Abstract 420

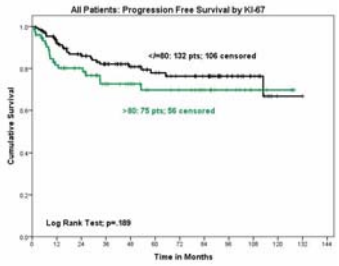
Sequential R-CHOP x 4/ICE x3: Overall and Progression Free Survival

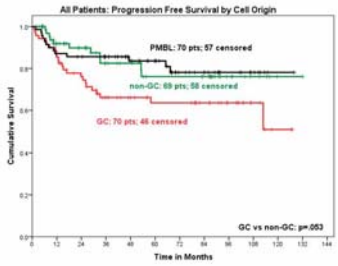


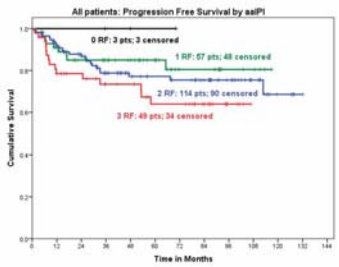


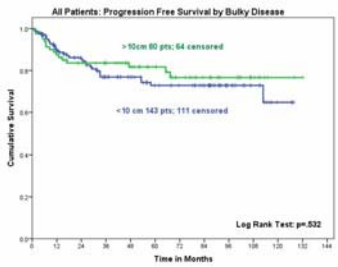
Moskowitz C, et al. Blood 2010;116:Abstract 420

Prognostic factors





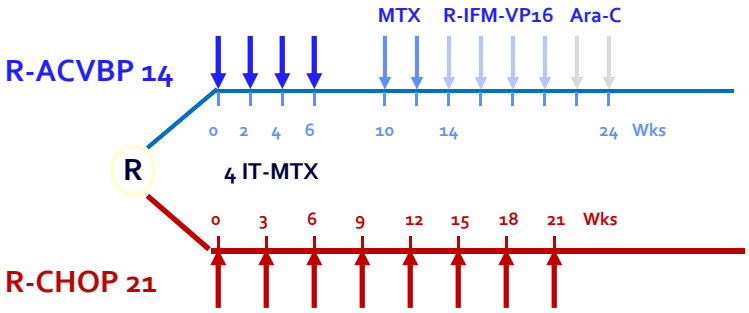




Moskowitz C, et al. Blood 2010;116:Abstract 420

LNH03-2B: R-ACVBP v R-CHOP

Patients: Untreated DLBCL, age 18-59, **aaIPI score =1** (high LDH, stage III/IV, ECOG PS >1)

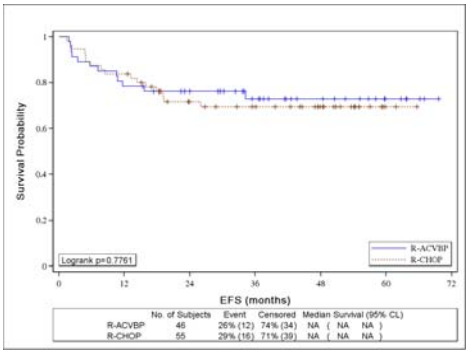


***No radiotherapy in both arms**

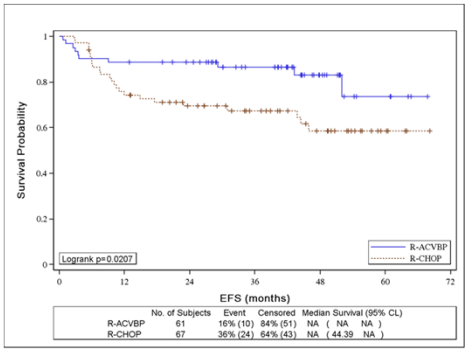
Recher et al. Lancet 2011 378: 1858–1867

LNH03-2B: Influence of Cell of Origin

Hans score=GC



Hans score=n-GC



Benefit of the dose dense sequential R-ACVBP appears to be limited to non-GC patients

Molina T. et al ASH Annual Meeting 2011; Abstract 2632

Comparison of R-CHOP/ICE and ACVBP with Consolidation

R-CHOP/ICE

Drug (cytotoxic)	DI mg/m²/wk	Total mg/m²
Rituximab	187.5	1500
Doxorubicin	25	200
Cyclosphosphamide	500	4000
Vincristine	0.7	5.6
Prednisone	*250	*2000
Ifosfamide	2500	15000
Etoposide	150	900
Carboplatin	**2.5	**15

ACVBP + Consolidation

Drug (cytotoxic)	DI mg/m²/wk	Total mg/m²
Rituximab	187.5	3000
Doxorubicin	37.5	300
Cyclophosphamide	600	4800
Vindesine	1	8
Bleomycin	*10	*80
Prednisone	150	1200
Methotrexate	1500	6000
Ifosfamide	750	6000
Etoposide	150	1200
Cytarabine	400	800

*FLAT dosing **Dose as AUC

Recher et al. Lancet 2011;378: 1858–1867, Moskowtiz et al J. Clin. Oncol. 2010; 28:1896-1903

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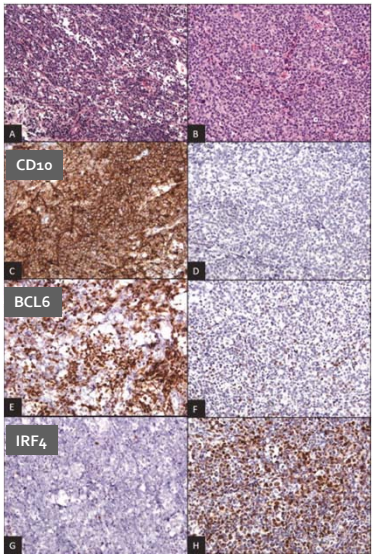
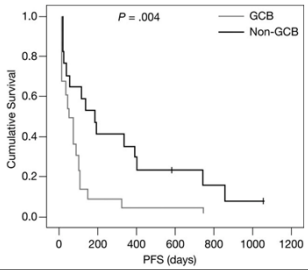
New Agents in DLBCL

Lenalidomide for DLBCL: Impact of Cell of Origin



	All	GCB	Non-GCB
Lenalidomide cycles			
Median (Range)	2 (1-35)	2 (1-21)	4 (1-35)
Response			
CR	6 (15.0)	1 (4.3)	5 (29.4)
PR	5 (12.5)	1 (4.3)	4 (23.5)
SD	7 (17.5)	7 (30.4)	0
PD	21 (52.5)	14 (60.9)	7 (41.2)
Unknown	1 (2.5)	0	1 (5.9)
ORR (CR + PR)	11 (27.5)	2 (8.7)	9 (52.9)
PFS, mo			
Median	2.6	1.7	6.2
95% CI	0.9-4.2	0.3-3.1	2.9-9.6



Hernandez-Ilizaliturri et al, Cancer 2011;117:5058

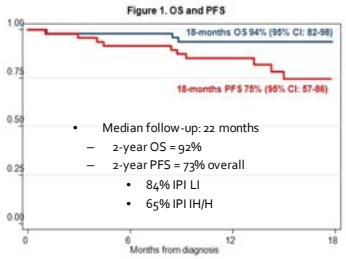
Frontline RL-CHOP in DLBCL or FL: Phase II Study Design

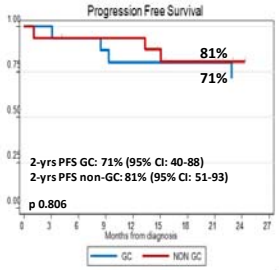
- Two trials with slightly different dose schedules of lenalidomide
- Compared with historical R-CHOP control (with similar baseline characteristics)

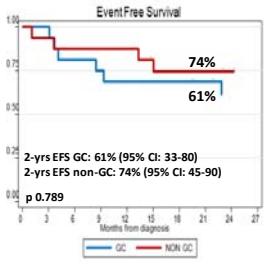
Chiappella et al. ASH 2012;Abstract 903; Nowakowski et al. ASH 2012;Abstract 689.

Lenalidomide + R-CHOP21 for Untreated DLBCL in Older Patients: Efficacy

Response	n (%)
ORR	45 (92)
CR	42 (86)
PR	3 (6)
SD	0
PD	3 (6)







Chiappella et al. ASH 2012;Abstract 903.

RL-CHOP vs R-CHOP Control Patients Characteristics

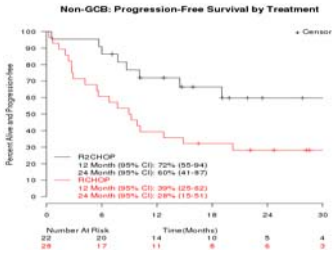
Characteristic	R2CHOP (N=64)	RCHOP (N=87)	p value
Age			0.01
Median (range)	65 (22-87)	61 (41-86)	
Gender			0.53
Male	40 (62.5%)	50 (57.5%)	
IPI			0.05
Low	7 (10.9%)	18 (20.7%)	
Low-Intermed.	24 (37.5%)	16 (18.4%)	
High-Intermed.	24 (37.5%)	38 (43.7%)	
High	9 (14.1%)	15 (17.2%)	
Ann Arbor Stage			0.04
2	7 (10.9%)	20 (23.0%)	
3	19 (29.7%)	14 (16.1%)	
4	38 (59.4%)	53 (60.9%)	
ECOG PS			0.36
0	30 (46.9%)	32 (36.8%)	
1	28 (43.8%)	41 (47.1%)	
2	6 (9.4%)	11 (12.6%)	
3	0 (0.0%)	3 (3.4%)	

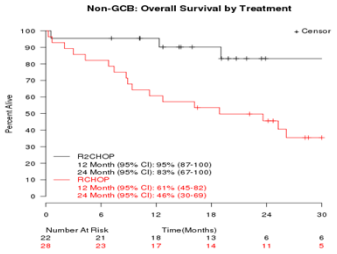
- 87 DLBCL consecutive contemporary patients treated with RCHOP
- Identified in MCR lymphoma database
- Same eligibility: stage 2-4 disease
- No major differences in clinical characteristics

Nowakowski et al. ASH 2012; ASCO 2014

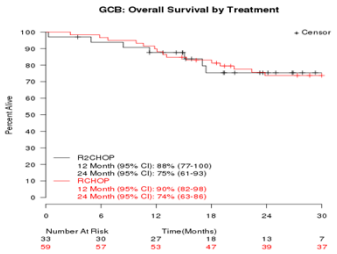
Outcomes for RL-CHOP v R-CHOP: Case Match Control by Cell of Origin

Non-GC DLBCL



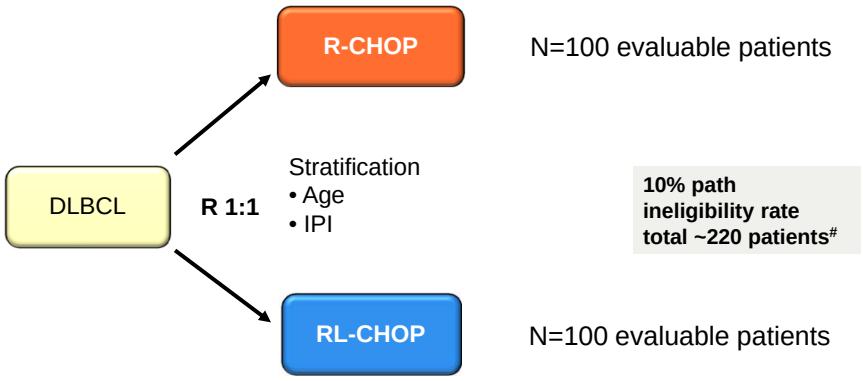


GC DLBCL



Nowakowski et al. ASH 2012; ASCO 2014

E1412: RL-CHOP vs. R-CHOP

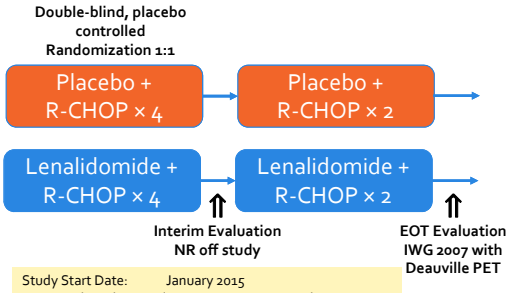


 # up to 300 patients can be enrolled to meet a goal of 50 ABC DLBCL patients per arm as defined by GEP

ROBUST (NCT02285062): Lenalidomide Plus R-CHOP Chemotherapy (R2-CHOP) Versus Placebo Plus R-CHOP Chemotherapy in Patients With Untreated ABC-DLBCL, Phase 3, double-blind, placebo-controlled

Inclusion
DLBCL, ABC-type, untreated COO by Lymph2Cx
Measurable disease by CT/MRI
ECOG 0-2
Age 18-80
IPI ≥2

Exclusion
Lymphoma other than DLBCL
HIV, HBV, HCV active infections
LVEF <45%
Peripheral neuropathy, grade ≥2
Other malignancies < 5 years disease free



Study Start Date: January 2015
Estimated Study Completion Date: September 2022
Estimated Primary Completion Date: June 2018

Sample Size/Statistical Plan
Sample size: 560
90% to detect increase in PFS of 60%

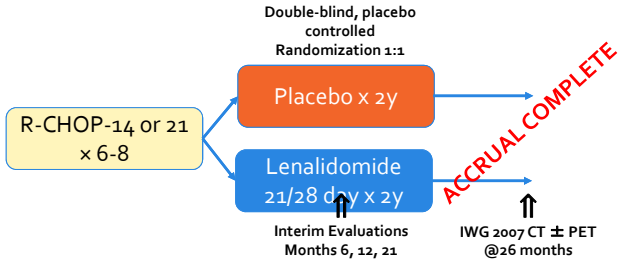
Evaluation
Interim evaluation after cycle 4
EOT (6 cycles) FDG-PET

Clinical Endpoints
Primary: Progression-free survival
Secondary: OS, CRR, Duration of CR, TTNT, ORR, QOL

REMARC (NCT01122472): Lenalidomide Maintenance Versus Placebo in Responding Elderly Patients With DLBCL and Treated With R-CHOP in First Line, Phase 3, double-blind, placebo-controlled

Inclusion
DLBCL treated with R-CHOP
PR or CR
ECOG 0-2
Age 60-80
IPI ≥1
Stage II-IV

Exclusion
Lymphoma other than DLBCL
Prior indolent lymphoma
MI within 3 months, unstable CAD, CHF III/IV
Active HIV, HBV, HBC
Other malignancies < 3 years disease free



Study Start Date: April 2009
Estimated Study Completion Date: September 2019
Estimated Primary Completion Date: September 2016

Sample Size/Statistical Plan
Sample size: 650
ACCRUAL COMPLETE

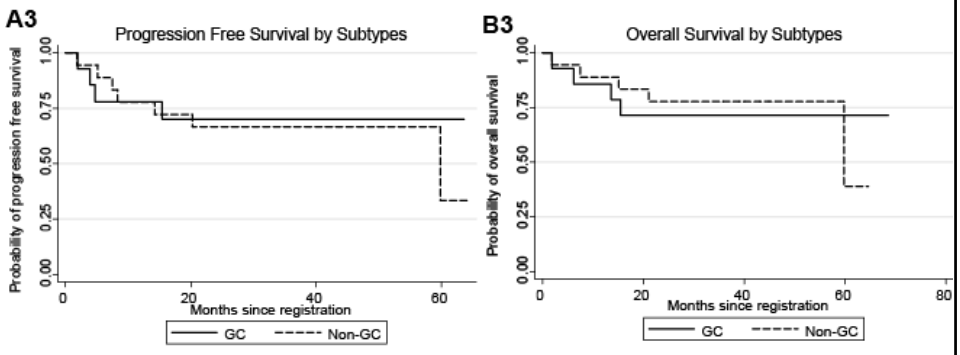
Evaluation
On maintenance evaluation: months 6, 12, 21
EOT: month 26 IWG 2007 CT ± PET

Stratifications
PR v CR
Cycles 6 v 8
Treatment interval 14 v 21

Clinical Endpoints
Primary: Progression-free survival
Secondary: Conversion PR to CR, efficacy by R-CHOP response, OS, safety

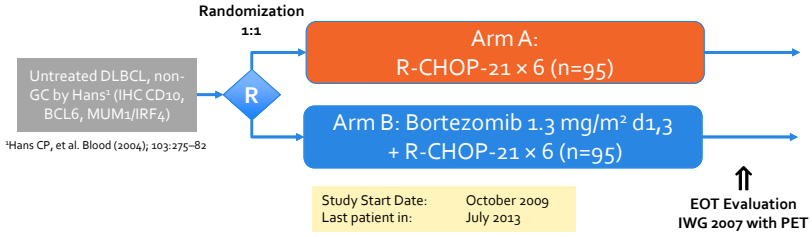
R-CHOP + Bortezomib DLBCL: PFS and OS by Subtype (n = 40)

- Treatment: Bortezomib 0.7 to 1.3 mg/m² on Day 1 and 4 of each R-CHOP-21 cycle
- Patient characteristics (n = 40):



Ruan J, et al. J Clin Oncol. 2010;29;690-97.

PYRAMID (NCT00931918): Randomized phase 2 open-label study of R-CHOP ± bortezomib in patients with untreated non-germinal center diffuse large B-cell lymphoma



Inclusion
DLBCL, non-GC, untreated (Hans)
Measurable disease
R-IPI ≥ 1
ECOG 0-2

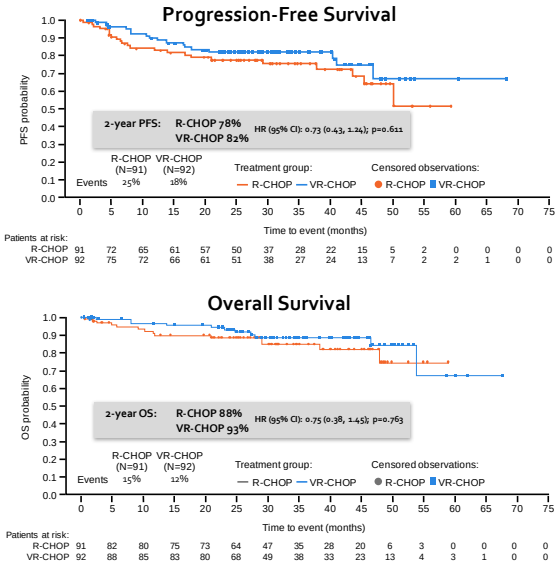
Evaluation
Interim evaluation after cycle 2 CT and FDG-PET
EOT (6 cycles) CT and FDG-PET
Study scans every 3 months

Clinical Endpoints
Primary: Progression-free survival
Secondary: OS, ORR, CRR, Safety

Sample Size/Statistical Plan
Sample size: 190
Success: Increase 2-y PFS from 62% to 75% (68 PFS events)

Leonard et al. ASH 2015; Abstract 811

PYRAMID (R-CHOP ± Bortezomib): Outcomes



No differences by IPI

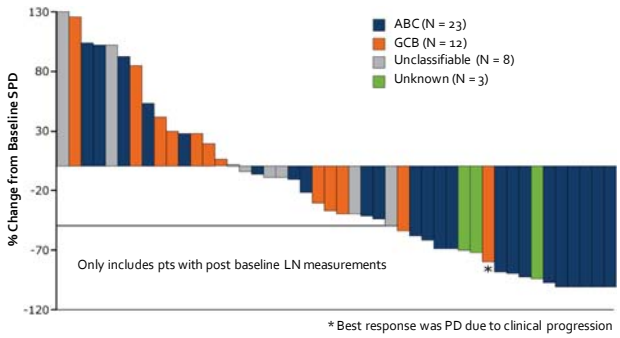
Leonard et al. ASH 2015;Abstract 811

Ibrutinib in Rel/Ref DLBCL: Phase II

Eligibility (N = 70)

- Relapsed/refractory de novo DLBCL
- Progressive disease (PD) after ASCT or ineligible for ASCT
- Archival tissue for central review
- No primary mediastinal DLBCL, transformed DLBCL or CNS involvement

→ Ibrutinib: 560 mg/d, PO



* Best response was PD due to clinical progression

Wilson WH et al. *ASH* 2012;Abstract 686.

R-CHOP + Ibrutinib: Phase 1b

Schema

PART 1: Newly diagnosed: FL, MCL, DLBCL	R-CHOP+Ibrutinib 3 dosing cohorts: 280 mg 420 mg 560 mg
PART 2: DLBCL only	R-CHOP+Ibrutinib 560 mg

R-CHOP x 6 cycles maximum; Ibrutinib dosed from daily starting day 3

- Dose reductions;
  - 4 patients required dose reduction of ibrutinib
    - Febrile neutropenia (FN) G3 (N=2)
    - Diarrhea G3 (N=1)
    - Prolonged bleed time (N=1)
  - 2 patients required dose reduction of doxorubicin due to FN
  - 7 patients required dose reduction of vincristine with the majority in cycle 4/5

- Efficacy (N=22)
  - ORR 100%: CR 91%, PR 9%
  - Non-GC DLBCL: CR 4/4
  - GC DLBCL: CR 12/14, PCR 2/14
  - Not assigned: CR 4/4

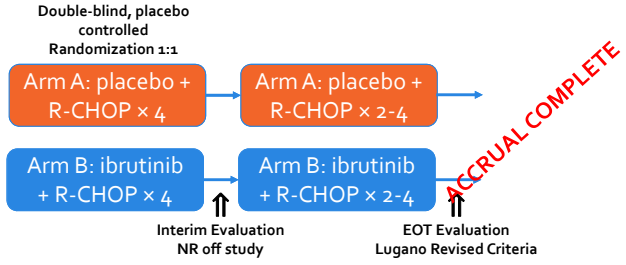
Younes et al. ASH 2013;Abstract 852

PHEONIX (NCT01855750): Ibrutinib in Combination With R-CHOP in Subjects With Newly Diagnosed Non-Germinal Center Diffuse Large B-Cell Lymphoma, Phase 3, double-blind, placebo-controlled

Inclusion
DLBCL, non-GC, untreated
Stage II (not candidates for RT), III, IV
≥1 measurable site
R-IPI ≥ 1
ECOG 0-2
LVEF WNL

Exclusion
Major surgery within 4 weeks
CNS disease
Prior indolent lymphoma
Warfarin
Concomitant CYP3A inhibitors

Sample Size/Statistical Plan
Sample size: 800
Study completion: 50% deaths or 7 years
ACCRUAL COMPLETE
Interim analysis after 270 EFS events
Cure 40 to 50%; HR for uncured 0.75



Study Start Date: September 2013
Estimated Study Completion Date: June 2020
Estimated Primary Completion Date: June 2018

Evaluation
Interim evaluation after cycle 4
EOT (6-8 cycles) FDG-PET

Stratifications
RIPI 1-2 v 3-5
US v Rest of World
6 v 8 cycles

Clinical Endpoints
Primary: Event-free survival
Secondary: PFS, OS, CRR, QOL, ibrutinib: clearance, volume of distribution, AUC, minimal concentration, AEs

Lymphoma Disease Management Team

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